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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/559,819	JURDIC ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2009 and 02 December 2009*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) *7-14,16,18,19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/2/09; 5/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 9/28/09 was entered.

Claims 1-14 and 16-21 are pending in the present application.

Claims 7-14, 16, 18-19 and 21 were withdrawn previously from further consideration because they are directed to non-elected inventions and non-elected species.

Therefore, amended claims 1-6, 17 and 20 are examined herein with the aforementioned elected species.

Response to Amendment

The rejection under 35 USC 101 because the claimed invention is directed to non-statutory subject matter was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(b) as being anticipated by Kikuchi et al. (Biomaterials 22:1705-1711, 2001; IDS) was withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claim 20 is vague and indefinite because of the phrase "wherein the osteoblasts and/or osteoclasts are normal, and wherein rheumatoid arthritis has been induced chemically in situ". Since the term "normal" is not defined by the instant specification, it is unclear based on which criteria that osteoblasts and/or osteoclasts are deemed to be normal or not normal. Additionally, what is the relevance of rheumatoid arthritis is induced chemically *in situ* with an *in vitro* bone system model of claim 1 containing "normal" osteoblasts and/or osteoclasts? Clarification is requested because the metes and bounds of the claim are not clearly determined as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are still rejected under 35 U.S.C. 102(b) as being anticipated by Van Blitterswijk et al. (US 6,152,964) for the same reasons already set forth in the Office action mailed on 2/13/09 (pages 5-6). ***The same rejection is restated below.***

Van Blitterswijk et al already disclosed an assay to examine the influence of osteoblast derived factors on osteoclastic resorption by culturing young rat osteoblasts on calcium phosphate samples (mineralized matrix), followed by the culture of young rat

osteoclasts (see at least example 3 in cols 5-6). Van Blitterswijk et al also disclosed that osteoclasts were present on the materials and resorption of the mineralized matrix formed by the osteoblasts was seen, and concluded that osteoclasts are capable of resorbing certain calcium phosphates but only when osteoblasts are firstly cultured on the substrates suggesting that factors produced by osteoblasts have a stimulating effect on osteoclastic activity. It is further noted that disclosed assay system taught by Van Blitterswijk et al mimics a human bone resorption system.

The teachings of Van Blitterswijk et al. meet all the limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 5/13/09 (pages 9-10) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the reference fails to disclose a co-culture of osteoblasts and osteoclasts; nor does the reference disclose the use of osteoblasts at confluence on the support. Applicants further argue that despite the fact that the reference described an in vitro system including bone cells such as osteoblasts and osteoclasts, there is no link between the objectives of the reference and the instant subject matter of the present application which is directed to an in vitro system that can be used as an in vitro diagnostic test for osteoclast transmigration.

First, Van Blitterswijk et al already disclosed an assay to examine the influence of osteoblast derived factors on osteoclastic resorption by **culturing young rat osteoblasts on calcium phosphate samples (mineralized matrix) for 18 days, followed by the culture of young rat osteoclasts** (see at least example 3 in cols 5-6). Van Blitterswijk et al also disclosed that osteoclasts were present on the materials and resorption of the mineralized matrix formed by the osteoblasts was seen, and concluded that **osteoclasts are capable of resorbing certain calcium phosphates but only when osteoblasts are firstly cultured on the substrates suggesting that factors produced by osteoblasts have a stimulating effect on osteoclastic activity**. It is apparent that the assay of Van Blitterswijk et al involves a co-culture of osteoblasts and osteoclasts. It is also noted that **there is no indication and/or suggestion that the initial cultured osteoblasts on calcium phosphate samples for 18 days were killed or removed prior to further culturing of osteoclasts**. Moreover, the culture of osteoblasts for 18 days on calcium phosphate samples would result in a layer of confluent osteoblasts and/or osteoblast nodules as evidenced at least by the teachings of Mulari et al (Calcif. Tissue Int. 75:253-261, 2004; IDS) disclosing that osteoblasts spread and formed multiple cell layers on bone slices as early as 3 days of culture (see at least page 255, col. 1, last paragraph and Fig. 2A).

Second, regardless of the main objective for the invention taught by Van Blitterswijk et al, the fact remains that the disclosed assay contains the same components as a bone system model as broadly claimed. Moreover, please also note

that for a composition claim, its intended use is not given patentable weight in light of the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) for the same reasons already set forth in the Office action mailed on 2/13/09 (pages 7-9). ***The same rejection is restated below.***

Shibutani et al already disclosed **a system comprising seeding osteoclasts on glass slides coated with apatite-collagen complexes (ACC) for measurement of osteoclastic resorption activity**, and found that osteoclasts could resorb the apatite particles and coated collagen on the glass slide (see at least the abstract and Materials and Methods section). Shibutani et al also teach that the ACC-coated glass slide could be useful for investigating both the function and metabolic activities of osteoclasts (page 159, col. 1, first paragraph).

Shibutani et al do not teach specifically a system comprising seeding osteoclasts on a layer of confluent osteoblasts and/or osteoblast nodules on a mineralized matrix for measurement of osteoclastic resorption activity.

At the effective filing date of the present application, Chamber et al already taught that **unmineralized osteoid is present on all bone surfaces, and that osteoclasts do not resorb bone from native bone surfaces** (see at least the Introduction section). Chamber et al also demonstrated **that calvarial cells (osteoblasts) are capable of osteoid destruction, and one mechanism by which osteoblasts induce osteoclastic bone resorption maybe though digestion of unmineralized organic material that covers bone surfaces, to expose the underlying resorption-stimulating bone mineral for osteoclastic contact (**see at least the abstract). Chamber et al further noted that **it is of interest that in a model of bone resorption in which osteoclasts can be induced to resorb bone simultaneously in a well-defined temporospatial sequence *in vivo***, the earliest observation, before multinucleate cells appear, is obliteration of unmineralized osteoid

from the bone surface; and that **a final common pathway for osteoblastic stimulation of osteoclastic bone resorption in response to local and systemic systems may be through proteolytic digestion of surface osteoid to expose bone mineral to osteoclastic contact** (see page 164, last two paragraphs).

Additionally, at the effective filing date of the present application Rovira et al also taught that **human osteoblasts are capable of attaching to and colonizing a calcium phosphate/elastin-solubilized peptide-collagen composite without loss of their phenotypic expression after 1 month in culture** (see at least the abstract and page 1535, col. 2, second full paragraph).

It would have been obvious for an ordinary skilled artisan to modify the osteoclastic resorption system of Shibutani et al by further coating the ACC-glass slides with a confluent layer of osteoblasts and/or osteoblast nodules prior to seeding the osteoclasts to model or mimic a bone resorption system on native bone surfaces to study metabolic activities of osteoclasts in light of the teachings of Chamber et al and Rovira et al as presented above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Chambers et al already taught that unmineralized osteoid is present on all bone surfaces, osteoclasts do not resorb bone from native bone surfaces and that one mechanism by which osteoblasts induce osteoclastic bone resorption is though digestion of unmineralized organic material that covers bone surfaces, to expose the underlying resoroption-stimulating bone mineral for osteoclastic contact. Moreover, Rovira et al also demonstrated that human osteoblasts are capable of attaching to and

colonizing a calcium phosphate/elastin-solubilized peptide-collagen composite without loss of their phenotypic expression after 1 month in culture.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al and Rovira et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 5/13/09 (pages 10-12) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the primary Shibutani et al reference does not teach or suggest the seeding of osteoclasts on a layer of osteoblasts at confluence; and that the Chambers reference does not cure the deficiencies of Shibutani because the Chambers reference is not directed to a bone model system, but rather explores mechanism by which osteoclasts effect bone resorption. Applicants also argue that the Chambers reference merely speculates that osteoblasts might play a role in osteoid destruction and that the reference itself acknowledges that "there was no evidence that such cells were capable of resorption of bone mineral…" (page 163, third paragraph). Applicants also argue that this speculation proved erroneous and that subsequent research has shown that osteoblasts do not participate in osteoid destruction; and one

skilled in the art would know that osteoblasts are not capable of osteoid destruction as evidenced by the statement "The osteoclast, which is a member of the monocyte/macrophage family, is the ***exclusive bone resorptive cell***, and its differentiation and activation are under the aegis of a variety of cytokines" in the abstract of Teitelbaum SL (Arthritis Res. Ther. 8(1):201, 2006); as well as the review articles of Karsenty, G (Genes & Development 13:3037-3051, 1999) and Komori T (J. Cell. Biochem. 99:1233-1239, 2006). Applicants further argue that the Rovira et al reference also fails to cure the deficiencies of Shibutani alone or in combination with Chambers because the reference does not describe a bone system model for diagnosing or assaying therapies for bone related maladies as claimed herein. The Rovira et al reference does not teach or suggest that osteoclasts seeded on a confluent layer of osteoblasts are capable of making their way through the joint population of osteoblasts. Lastly, Applicants that none of recited references discloses or suggests that osteoblasts, which are ten times the size of osteoblasts, could or could not be expected to migrate through the joint population of osteoblasts to effect resorption activity directly on the bone matrix; and without such an understanding or expectation, there would have been no reasoned basis for constructing or employing the system as claimed.

First, please note that the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. Additionally, it appears that Applicants considered the teachings of each of the cited references in total isolation one from the others. Furthermore, KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a

finding of obviousness. See the recent Board decision *Ex parte Smith*, - - USPQ2d - -, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396).

Second, Chambers stated explicitly "We have found that both resident bone cells and neonatal calvarial cells are able to digest osteoid *in vitro*. Among the cell types present in our cultures, ***cells of the osteolastic lineage may be responsible; they are known to produce collagenase and plasminogen activator, and produce increased amounts of both in response to agents that stimulate bone resorption***"; "***A causal role for cells of the osteoblastic lineage in osteoid destruction in our cultures is further suggested by the hormone-dependent nature of the process, since osteoblast appear to be the cell type in bone with PTH receptors***...One report (Rao, Murray & Heerche, 1983) additionally describes PTH receptors on osteoclasts, ***but the osteoid destruction we have described is unlikely to be due to osteoclastic cells in the calvarial cell digests since we detected no evidence of mineral resorption typical of osteoclasts***" (page 163, third paragraph); and "Many of the agents that stimulate osteoclastic bone resorption appear not to stimulate osteoclasts directly..., ***but do exert morphological and functional effects on osteoblasts***...; ***this suggests that osteoblasts play a major role in the control of osteoclastic bone resorption***. ***One of the effects that stimulators of bone resorption have on osteoblasts is enhancement of secretion of collagenase and plaminogen activator*** (Sakamoto & Sakamoto, 1982; Heath et al. 1984). ***A final common pathway for osteoblastic stimulation of osteoclastic bone resorption in response to local and systemic influences may be through proteolytic digestion***

of surface osteoid to expose bone mineral to osteoclastic contact" (page 164, last paragraph). These cited statements support the findings of Chambers and other research groups at the effective filing date of the present application that osteoblasts play a major role in the control of osteoclastic bone resorption; and a final common pathway for osteoblastic stimulation of osteoclastic bone resorption in response to local and systemic influences may be through proteolytic digestion of surface ostoid to expose bone mineral to osteoclastic contac.

Third, with respect to the abstract of Teitelbaum SL and the review articles of Karsenty, G and Komori T, it is noted that none of these cited references concerns specifically about the role of osteoblasts in osteoclastic bone resorption, nor any of these references provide any factual evidence to refute the findings of Chambers and many of the prior art cited by Chambers. Additionally, Mulari et al (Calcif. Tissue Int. 75:253-261, 2004; IDS) demonstrated that osteoblasts are capable of removing organic matrix in resorption lacunae which were first created by osteoblasts (see at least the abstract; sections titled "Osteoblast-like cells are able to complete organic matrix degradation" and "Macrophages do not remove organic residual matrix from the lacunae"). Furthermore, Van Blitterswijk et al (US 6,152,964) also disclosed that osteoclasts were present on the materials and resorption of the mineralized matrix formed by the osteoblasts was seen, and concluded that osteoclasts are capable of resorbing certain calcium phosphates but only when osteoblasts are firstly cultured on the substrates suggesting that factors produced by osteoblasts have a stimulating effect on osteoclastic activity.

Fourth, please note that both osteoclasts and osteoblasts can migrate, and that osteoblasts play a major role for the control of osteclastic bone resorption as evidenced at least by the teachings of Chambers and US 6,152,964 as discussed above; and therefore regardless of the size of osteoclasts and/or the exact migrating mechanism an ordinary skilled artisan would reasonably expect that the cultured osteoclasts in the modified system of Shibutani et al, Chambers et al. and Rovira et al as set forth above could resorb the underlying mineralized matrix. Moreover, a bone system model as claimed simply recites to contain the following components: a mineralized matrix, a layer of osteoblasts and/or nodule of osteoblasts at confluence on the matrix and osteoclasts deposited on the osteoblast layer and/or nodule.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Traianedes et al. (Endocrinology 139:3178-3184; IDS) for the same reasons already set forth in the Office action mailed on 2/13/09 (pages 10-11). ***The same rejection is restated below.***

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches further inducing rheumatoid arthritis in the modified bone system by chemically *in situ*.

At the effective filing date of the present application, Traianedes et al already taught that **application of exogenous leukotriene *in vitro* and *in vivo* results in increased osteoclast formation and resorption, and that 5-lipooxygenase (5-LO) metabolites also inhibit bone and/or bone nodule formation on cell cultures** (see at least the abstract). Traianedes et al further disclosed that **5-LO metabolites may be responsible for decreased osteoblast function or decreased bone formation in conditions of elevated 5-LO metabolite production such as the acute phase inflammatory response and rheumatoid arthritis** (page 3182, col. 2, last two lines continue to first paragraph of col. 1 on page 3183).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by introducing exogenous leukotriene or 5-LO metabolites into the modified model of bone resorption to mimic the conditions found in rheumatoid arthritis to study metabolic activities of osteoclasts.

An ordinary skilled artisan would have been motivated to carry out the above modification because Traianedes et al already disclosed that production of 5-LO metabolites are elevated in rheumatoid arthritis.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Traianedes et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 5/13/09 (pages 12-13) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the Traianedes reference fails to cure the deficiencies of the combined references Shibutani, Chambers and Rovira for the reasons discussed in the rejection of claims 1-4. The Traianedes reference does not present any data on the capacity of osteoclasts to transmigrate.

Once again, the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. For example, the Traianedes reference does not have to present any data on the capacity of osteoclasts to transmigrate. With respect to the deficiencies of the combined references Shibutani, Chambers and Rovira, please refer to the examiner's responses to Applicant's arguments in the rejection of claims 1-4 above. The teachings of Traianedes were used to supplement the combined teachings of Shibutani, Chambers and Rovira for the introduction of exogenous leukotriene or 5-LO metabolites into the modified model of bone resorption to mimic the conditions found in rheumatoid arthritis to study metabolic activities of osteoclasts.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Rodan et al. (US 6,093,533) for the same reasons already set forth in the Office action mailed on 2/13/09 (pages 11-12). ***The same rejection is restated below.***

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches the use of the system for testing or assaying a substance.

At the effective filing date of the present application, Rodan et al already taught the use of an assay comprising an osteoclast-enriched population of cells containing osteoblasts on a bone slice to test inhibitory or stimulatory effect of a test substance, including a drug that inhibits bone resorption (see at least col. 5, lines 38-56).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by also using the modified osteoclastic resorption system to test inhibitory or stimulatory effect of a test substance as well as for a drug that inhibits bone resorption.

An ordinary skilled artisan would have been motivated to carry out the above modification because Rodan et al already taught successfully using an assay comprising an osteoclast-enriched population of cells containing osteoblasts on a bone slice to test inhibitory or stimulatory effect of a test substance.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Rodan et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 5/13/09 (pages 13-14) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the Rodan reference fails to cure the deficiencies of the combined references Shibutani, Chambers and Rovira for the reasons discussed in the rejection of claims 1-4. The Rodan reference does not disclose an example of assaying compounds on a population as recited in the instant claims, e.g., mineralized matrix, layers or nodules of osteobalsts, and a layer of osteoclasts.

Once again, the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. For example, the Rodan reference does not have to disclose an example of assaying compounds on a population as recited in the instant claims. With respect to the deficiencies of the combined references Shibutani, Chambers and Rovira, please refer to the examiner's responses to Applicant's arguments in the rejection of claims 1-4 above.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Choi et al. (US 2004/0092714) for the same reasons already set forth in the Office action mailed on 2/13/09 (pages 12-13). ***The same rejection is restated below.***

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches the use of genetically modified osteclasts.

At the effective filing date of the present application, Choi et al already taught a method for modulating osteoclast activities comprising contacting an osteoclast cell with a compound that modulates activity of an OSCAR (osteoclast associated receptor) that includes an antisense, ribozyme and triple-helix forming nucleic acid (see at least paragraph 14).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by also studying metabolic activities of osteoclasts transformed or transfected with compounds such as antisense, ribozyme and triple-helix forming nucleic acid specific against OSCAR gene (such cells would fall within the broad scope of osteoclasts being genetically modified)

on the modified system that mimicks native bone surface in light of the teachings of Choi et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Choi et al already taught that compounds such as antisense, ribozyme and triple-helix forming nucleic acid specific against OSCAR gene could modulate osteoclast cell activities.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Choi et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 5/13/09 (page 14) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the Choi reference fails to cure the deficiencies of the combined references Shibutani, Chambers and Rovira for the reasons discussed in the rejection of claims 1-4. The Choi reference does not disclose or suggest any system as defined in claim 1

With respect to the deficiencies of the combined references Shibutani, Chambers and Rovira, please refer to the examiner's responses to Applicant's arguments in the

rejection of claims 1-4 above. The teachings of Choi et al. were used to supplement the combined teachings of Shibutani, Chambers and Rovira for studying metabolic activities of osteoclasts transformed or transfected with compounds such as antisense, ribozyme and triple-helix forming nucleic acid specific against OSCAR gene (such cells would fall within the broad scope of osteoclasts being genetically modified) on the modified system that mimicks native bone surface.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Sun et al. (Biomed. Mater Res. 45:311-321, 1999; IDS) for the same reasons already set forth in the Office action mailed on 2/13/09 (pages 14-15). ***The same rejection is restated below.***

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches the use of osteoclasts to osteoblasts in the ratio of approximately 1/10 to 1/25.

At the effective filing date of the present application, Sun et al already studied the influence of hydroxyapatite particles on osteoclast cell activities in an *in vitro* osteoblast/osteoclast co-cultured model in which the ratio of osteoclasts/osteoblasts in initial cultures start from about 8.6%, within the range of 1/10 to 1/25 ratio as claimed

(see at least the abstract; Table II and page 314, col. 1, last two lines continue to the paragraph of col. 2).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by also using the ratio of osteoclasts/osteoblasts from approximately 1/10 to 1/25 in the modified bone resorption system.

An ordinary skilled artisan would have been motivated to carry out the above modification because Sun et al already used successfully an osteoblast/osteoclast co-cultured model in which the ratio of osteoclasts/osteoblasts in initial cultures starts from about 8.6% to test the influence of hydroxyapatite particles on osteoclast cell activities.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Sun et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 5/13/09 (page 15) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the Sun reference fails to cure the deficiencies of the combined references Shibutani, Chambers and Rovira for the reasons discussed in

the rejection of claims 1-4. The Sun reference does not disclose or suggest a system as recited in claim 1, but merely discloses the effect of hydroxyapatite size on the ratio of osteoblasts/osteoclasts.

With respect to the deficiencies of the combined references Shibutani, Chambers and Rovira, please refer to the examiner's responses to Applicant's arguments in the rejection of claims 1-4 above. The teachings Sun et al. were used to supplement the combined teachings of Shibutani, Chambers and Rovira for using the ratio of osteoclasts/osteoblasts from approximately 1/10 to 1/25 in the modified bone resorption system.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633